Response Under 37 CFR §1.116
Expedited Procedure
Examining Group 1634

CASE 4-32702A

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KUDARAVALLI ET AL.
APPLICATION NO: 10/529,613
35 USC §371 DATE: JUNE 8, 2005
FOR: METHODS TO TREAT CHOLESTEROL ELEVATIONS DURING IMMUNOSUPPRESSANT THERAPY

Art Unit: 1634
Examiner: Pohnert, Steven C

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER FINAL REJECTION

Sir:

This Amendment and Response is submitted in response to the Office Action mailed June 16, 2009 and the Advisory Action mailed November 6, 2009. A petition for a one month extension of time was included with the response filed October 15, 2009 and a second month extension (i.e., to November 16, 2009) was included with the response filed November 4, 2009. Accordingly, a third month petition is included herewith (i.e., to December 16, 2009). Fees may be charged to deposit account 19-0134 in the name of Novartis.

Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the Specification

Please amend the first paragraph under the heading "Summary of the Invention" on page 2 of the specification as follows:

The present invention overcomes this problem by providing a method to determine the degree of serum cholesterol elevation which will occur in a patient during treatment with an immunosuppressant medication comprising: determining for the two copies of the IL-1 β gene present in the patient the identity of the nucleotide pair at the polymorphic site -511 C T (position 1423 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing) of the IL-1 ß gene; and assigning the patient to a high cholesterol elevation group if both pairs are AT, assigning the patient to an intermediate cholesterol elevation group if one pair is AT and one pair is GC and assigning the patient to a low cholesterol elevation group if both pairs are GC.

Please amend the first paragraph on page 3 of the specification as follows:

In a further embodiment this invention provides another method to treat a patient with an immunosuppressive medication comprising: determining for the two copies of the IL-1 β gene present in the patient the identity of the nucleotide pair at the polymorphic site - 511 C T (position 1423 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing) of the IL-1 ß gene; and treating the patient with the immunosuppression medication if both pairs are GC and using alternative treatment if one pair is AT and one pair is GC or if both pairs are AT. The immunosuppressive medication may be selected from the list in Table 2 and may be everolimus. In addition this invention provides that the alternative treatment comprises the addition of a cholesterol-lowering medication chosen from those listed in Table 1.

Please amend the second paragraph on page 3 of the specification as follows:

In a further embodiment this invention provides a method to determine the degree of serum cholesterol elevation which will occur in a patient during treatment with an immunosuppressant medication comprising: determining for the two copies of the IL-1 ß gene present in the patient the identity of the nucleotide pair at the polymorphic site -31 T C (position 1903 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing) of the IL-1 ß gene; and assigning the patient to a high cholesterol elevation group if both pairs are CG, assigning the patient to an intermediate cholesterol elevation group if one pair is AT and one pair is GC and assigning the patient to a low cholesterol elevation group if both pairs are AT.

Please amend the third paragraph on page 3 of the specification as follows:

In a still further embodiment this invention provides a method to treat a patient with an immunosuppressive medication comprising: determining for the two copies of the IL-1 ß gene present in the patient the identity of the nucleotide pair at the polymorphic site -31 T C (position 1903 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing) of the IL-1 ß gene; and treating the patient with the immunosuppression medication if both pairs are AT and using alternative treatment if one pair is AT and one pair is GC or if both pairs are CG. The immunosuppressive medication may be selected from the list in Table 2 and may be everolimus. In addition the alternative treatment may comprise the addition of a cholesterol-lowering medication chosen from those listed in Table 1.

Please amend the paragraph bridging pages 5-6 of the specification as follows:

In one embodiment, a patient who is a potential candidate for treatment with an IM would have blood drawn for a determination of the presence of a polymorphism, i. e., cytosine (C) thymine (T) at nucleotide position -511 (in the promoter region with no amino acid change) ; this is a C T change at nucleotide position 1423 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing, in the two copies of the interleukin-1-beta (IL-1 ß) gene present in the patient. If the nucleotide pair at position -511 is AT in both copies of the gene, then the patient will experience a high elevation in serum cholesterol levels during treatment with an IM.

Please amend the paragraph bridging pages 6-7 of the specification as follows:

In a further embodiment, a patient who is a potential candidate for treatment with an IM would have blood drawn for a determination of the presence of a polymorphism T C at nucleotide position -31 (in the promoter region with no amino acid change); this is a T C change at nucleotide position 1903 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing, in the two copies of the IL-1 ß gene present in the patient. If the nucleotide pair at position -31 is a CG in both copies of the gene, then the patient will experience a high elevation in serum cholesterol levels during treatment with an IM. If the nucleotide pair at position -31 is AT in one copy and CG in the other copy, then the patient will have an intermediate elevation in their cholesterol levels during treatment with an IM. If the nucleotide pair is AT at both copies at position-31, then the patient will have a low elevation in serum cholesterol levels during treatment with an IM.

Please amend the third paragraph on page 24 of the specification as follows:

As used herein, the term "haplotype with regard to the IL-1 ß gene" shall refer to the haplotype consisting of the combination of the polymorphisms at the -511 and the -31 position of the IL-1 ß gene and these haplotypes shall be named in the following manner; the haplotype shall be called "high cholesterol" if both the C to T polymorphism at the polymorphic site -511 of the IL-1 ß gene (position 1423 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing) and the T to C polymorphism at the polymorphic site -31 of the IL-1 ß gene (position 1903 of sequence X04500, which is incorporated by reference and is SEQ ID NO:11 of the sequence listing) are present in one copy of the IL-1 ß gene. Conversely, the haplotype shall be called "low cholesterol" if both these polymorphisms are not present in a given copy of the IL-1 ß gene and therefore the nucleotide at site -31 of this IL-1 ß gene is a T and the nucleotide at site -511 is a C in this IL-1 ß gene in the chromosome referred to.